Amer J Hum Genet 25:446–456, 1973

Analytic Review:

Phenotypic Diversity of Human Diseases Resulting from Allelic Series

VICTOR A. MCKUSICK[1]

The Hurler and Scheie syndromes have widely different clinical features and were thought to be unrelated mucopolysaccharidoses, numbered I and V, respectively [1]. However, the work of Neufeld and her colleagues compels the conclusion [2] that these may be allelic disorders. Earlier work showed that the same "corrective factor" is missing in the two conditions [3], and subsequently both conditions have been found to have a deficiency of α-L-iduronidase [4]. The first three editions of my ***Mendelian Inheritance in Man*** [1], which intends to assign one asterisked* entry per genetic locus, carried separate asterisked entries for MPS I and MPS V. This experience prompted a survey of genetic diseases in search of other examples of clinically disparate phenotypes which may represent allelic disorders. At the same time, the validity of the methods for identifying allelism versus nonallelism has been examined.

A wide range and diversity of phenotypes can be produced by allelic series, as shown (1) in experimental species such as the mouse where controlled matings permit reasonable proof of allelism, and (2) in man for loci such as those for the polypeptide chains of the hemoglobins where the findings of amino acid sequencing substitute for controlled matings in providing this proof. Genes known to be allelic because they determine structural variants of the β chain of hemoglobin produce phenotypes as disparate as cyanosis (e.g., Hb $\mathrm{M_{Saskatoon}}$), polycythemia (e.g., Hb Malmö), and anemia, either persistent with painful crises (e.g., Hb S) or intermittent, drug induced (e.g., Hb Zürich). Were it not for the biochemical evidence for allelism, these would likely be listed as separate entries in ***Mendelian Inheritance in Man,*** just as the Hurler and Scheie syndromes were.

Further phenotypic diversity is provided by genetic compounds†—the condition

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Received January 3, 1973; revised January 30, 1973.

Work related to this review is supported in part by U.S. Public Health Service grant GM 19489 from the National Institutes of Health for the support of a Center in Medical Genetics.

[1] Division of Medical Genetics, Department of Medicine, Johns Hopkins University School of Medicine and Johns Hopkins Hospital, Baltimore, Maryland 21205.

* The asterisked entries are those relating to phenotypes for which the particular mode of inheritance seems quite certain and no other asterisked entry has wittingly been made for that locus.

† Otherwise known as "mixed heterozygotes," "compound heterozygotes," or "allozygotes"

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when two different rare alleles are present at a given locus. Again a cardinal example is provided by the hemoglobinopathies: SC disease has a phenotype distinctive from both of the homozygous states SS and CC. Compounds of the Hurler and Scheie genes are also thought to occur [2] producing a phenotype intermediate between those of the homozygotes. In the presumed compounds, deficiency of iduronidase is demonstrable. An increased frequency of parental consanguinity is not observed and is not to be expected in these cases. As the frequency of consanguineous marriages declines in our society, the relative importance of genetic compounds in clinical genetics increases. (It is possible, of course, that cases of intermediate phenotype judged to be the compound heterozygote are in fact homozygotes for yet another allele at the same locus.)

Table 1 presents a list of conditions which have more than one phenotypic variety that can with some validity be suspected of being allelic, even though in many instances the phenotypes are rather strikingly different. Those conditions in which one or more genetic compounds have with good reason been suspected are starred. I have in the past expressed my dislike for statements such as "disease A is a variant of disease B" [5]. If the expression is to be used at all it would seem most appropriate for these allelic disorders. The primary criterion for inclusion in table 1 was the existence of reasonably striking phenotypic differences. Not included here are some disorders in which occult genetic heterogeneity is revealed by special methods such as tests for cross-reacting material or electrophoretic differences in the relevant protein.

EVIDENCE FOR ALLELISM

In all the conditions listed in parts I,A and II,A of table 1, the basic defect is known, at least in terms of a specific enzyme function, and the conclusion of allelism is based on the fact that the same enzyme function is deficient. This is not firm evidence for allelism because several steps are likely to be concerned in enzyme realization, each under separate genetic control; by enzyme realization Paigen [6] means the entire multicomponent process by which the enzyme's final phenotype—regulation of synthesis, localization in the cell, tissue distribution, substrate specificity, stability, cofactor requirements, catalytic kinetics, activation—is achieved. Moreover, the enzyme may have two or more structurally different subunits each under separate genetic control.

The occurrence of different subunits in enzymes is a rather frequent phenomenon. Often one polypeptide subserves the main catalytic function, whereas the other has a controlling or other role such as binding to substrate, entry into or localization in the cell, or binding of cofactor or allosteric inhibitors. Each of the two polypeptide chains of tryptophane synthetase in *Escherichia coli* has distinctive enzymatic properties, but catalytic activity is maximal only when they interact. Single-chain enzymes probably are not subject to allosteric regulation [7]. Thus, the multichain enzymes represented a giant step forward in the evolution of regula-

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(G. A. Chase, personal communication, 1972), but not "double heterozygotes," a term which from long usage is reserved to mean heterozygosity at two different loci.

TABLE 1

PHENOTYPIC DIVERSITY BASED ON ALLELIC SERIES (DISORDERS WITH TWO OR MORE CLINICALLY DISTINCTIVE FORMS SUSPECTED OF BEING ALLELIC)

I. Autosomal
A. Enzyme (or other protein) deficiency known
1. Acatalasia—20020
2. Acid phosphatase deficiency—20095
3. Adrenogenital syndrome due to 21-hydroxylase deficiency—20170
4. Afibrinogenemia—20240
5. Alpha-1-antitrypsin deficiency—10740
6. Argininosuccinic-aciduria—20790
7. Cystathioninuria (cystathionase deficiency)—21950
8. Farber lipogranulomatosis—22800
9. Fucosidosis (α-L-fucosidase deficiency)—23000
*10. Galactosemia (galactose-1-phosphate uridyl transferase deficiency)—23040
*11. Gaucher disease (glucocerebrosidase deficiency)—23080, 23090, 23100
*12. Glucosephosphate isomerase deficiency—17240
13. Glycogen storage disease I (glucose-6-phosphatase deficiency)—23220
14. Glycogen storage disease II (alpha-1,4-glucosidase deficiency)—23230
15. Homocystinuria—23620
16. Hypophosphatasia—24150
17. Maple syrup urine disease (keto acid decarboxylase deficiency)—24860
*18. Metachromatic leukodystrophy (cerebroside sulfatase deficiency)—25000, 25010 25020
19. Methylenetetrahydrofolate reductase deficiency—23625
*20. MPS I—25240
21. MPS VI—25320
22. Neuronal ceroid-lipofuscinoses—20420, 20430, 20450
23. Niemann-Pick disease (sphingomyelinase deficiency)—25720
24. Phenylketonuria (phenylalanine hydroxylase deficiency)—26160
*25. Pseudocholinesterase deficiency—27240
*26. Pyruvate kinase deficiency hemolytic anemia—26620
27. Tay-Sachs disease (hexosaminidase A deficiency)—27280
28. Vitamin B12 metabolic defect—27740
29. Wolman disease; cholesterylester storage disease—27800
30. Xeroderma pigmentosum—27870, 27880

B. Enzymatic or other molecular basis not yet known
*1. Achondroplasia—10080
2. Cataract, autosomal dominant forms—11570, 11580, 11590
3. Cystic fibrosis—21970
*4. Cystinosis—21980, 21990, 22000
*5. Cystinuria—22010
6. Diastrophic dwarfism—22260
7. Ehlers-Danlos syndrome—13000
*8. Epidermolysis bullosa—13170, 22650, 22660
9. Fanconi renotubular syndrome—22770, 22780
*10. Infantile cystic kidney—26320
11. Keratosis palmaris et plantaris with esophageal cancer
12. Morquio syndrome—25300
13. Myotonic dystrophy—16090
14. Renal glycosuria—23310
15. Spinal muscular atrophy—25330, 25340
16. Von Recklinghausen neurofibromatosis—16220, 10100
II. X-linked
A. Enzyme (or other protein) deficiency known
1. Fabry angiokeratoma—30150
2. Glucose-6-phosphate dehydrogenase deficiency—30590
3. Hemophilia A—30670
4. Hemophilia B—30690

TABLE 1 (continued)

   5. Hypoxanthine-guanine phosphoribosyltransferase deficiency—30800
   6. MPS II—30990
   7. Thyroid-binding globulin variants—31420

B. Molecular basis unknown
   1. Colorblindness, deutan—30380
   2. Colorblindness, protan—30390
   3. Ichthyosis—13810
   4. Ocular albinism—30050, 30060
   5. X-linked deafness—30440, 30450, 30460
   6. X-linked muscular dystrophies—31000, 31010, 31020, 31030

NOTE.—Five-digit numbers refer to numbers of entry in [1].

* Genetic compounds demonstrated or suspected with good reason. Compound heterozygotes are, of course, not likely to be observed in the case of rare X-linked traits.

tion. Aspartate transcarbamylase, which has been studied extensively in *E. coli*, has two types of polypeptide chains. One determines the specific catalytic activity, whereas the other is regulatory having a strong affinity for cytidine triphosphate, a negative feedback inhibitor [8]. A good example of a heteromeric enzyme in man is lactose synthetase, found only in lactating mammary glands. Its A chain is N-acetyl-lactosamine synthetase, an enzyme which is bound to the membranes of the Golgi system in many tissues, not only breast, and which in the other tissues, without the B chain, functions in the synthesis of the carbohydrate part of glycoproteins. The B chain of lactose synthetase is lactalbumin, a principal protein of milk. It has structural similarities to lysozyme indicating a closer evolutionary kinship than that between hemoglobin and myoglobin. By itself, the B chain has no known enzymatic function. In combination with the A chain it determines the enzymatic specificity of lactose synthetase [9]. Hormonal regulation of lactose production is through control of the synthesis of lactalbumin.

In table 2 are listed six enzymes which have two structurally different subunits (at least in some organisms in which studies have been possible) and which are deficient in specific genetic diseases of man of which two or more phenotypically distinct forms may exist. These can be cited as possible examples of a nonallelic

TABLE 2

ENZYMES WITH HETEROMERIC STRUCTURE IMPLICATED IN HUMAN DISEASE*

Enzyme	Structure	Source
Rat liver cystathionine synthetase	$\alpha_2\beta_2$	[11]
Human plasma factor XIII	$\alpha_2\beta_2$	[12]
Rat liver α-L-fucosidase	$\alpha_2\beta_2$	[13]
Rabbit liver fructose-1,6-diphosphatase	$\alpha_2\beta_2$	[14]
Escherichia coli carbamylphosphate synthetase	$\alpha\beta$	[15]
Human placental and leukocyte acid phosphatase	$\alpha\beta$	[16]

* From I. M. Klotz (personal communication, 1972) and [10].

basis of the phenotypic diversity with which we are concerned here. The enzymes which are implicated in many of the other diseases listed in table 1 are known to have only one species of subunit (I. M. Klotz, personal communication, 1972; [10]).

Homocystinuria (cystathionine synthetase deficiency) exists in at least two forms: a B_6-responsive form, usually with normal intellect, and a B_6-nonresponsive form [17]. If human cystathionine synthetase has an $\alpha_2\beta_2$ structure similar to the rat liver enzyme (table 2), then the two forms of homocystinuria might be produced by nonallelic mutations. The $\alpha_2\beta_2$ structure of Factor XIII (table 2) is of particular interest because both an X-linked (30550)* and an autosomal recessive (22850) form of Factor XIII deficiency may exist [18]. Fucosidosis (23000) of several different phenotypes has been observed. Some patients have a Hurler-like phenotype [19] whereas others have severe mental and physical retardation but do not resemble the Hurler syndrome [20]. Patel, Watanable, and Zeman [21] found skin lesions like those of Fabry disease (30150), that is, angiokeratoma corporis diffusum, in their 20-year-old patient with fucosidosis. Puzzling is the finding of Schafer, Powell, and Sullivan [22] of deficiency of α-L-fucosidase in fibroblasts from a child with an unusual spondylometaphyseo-epiphyseal dysplasia but normal intelligence. Among the few cases of fructose-1,6-diphosphatase deficiency (22970) no heterogeneity has, to my knowledge, come to light. Carbamylphosphate synthetase deficiency (23730) is a form of hyperammonemia, a defect of the urea cycle. Here, too, phenotypic heterogeneity is not established, but this may be merely due to the fact that scarcely more than one patient has been identified [23]! Acid phosphatase deficiency occurs in at least two phenotypically distinct forms (H. L. Nadler, personal communication, 1972). The discovery of a heteromeric structure of placental and leukocytic acid phosphatase [16] is consistent with a nonallelic interpretation for these two forms of disease (if the forms of acid phosphatase which are deficient in the disease are also heteromeric).

In addition to multiple different subunits as a possible mechanism of nonallelic deficiency in the function of one and the same enzyme protein, some critical post-translational change in the protein may fail to take place because of mutation. For example, it may be necessary for some part of the molecule to be cleaved off to render it functionally active, just as the registration (or coordination) peptide must be cleaved from procollagen to produce functionally normal collagen [24]. Or addition of some prosthetic groups may be essential to catalytic or other functions of the enzyme, just as, according to the postulation of Hickman and Neufeld [25], carbohydrate side chains added to multiple lysosomal hydrolases ensure reentry to cells, the mechanism for this modification being defective in I-cell disease (25250). If it were not for the difference in mode of inheritance (X-linked recessive and autosomal dominant, respectively) hemophilia A (30670) and von Willebrand disease (19340) might be listed in table 1 as possibly allelic disorders because deficiency of Factor VIII is present in both. The nonallelic nature is supported by the fact that plasma from patients with hemophilia A corrects [26] the clotting defect in patients with von Willebrand disease (although the converse is not true). After a brief lag period, the Factor VIII level rises in patients with von Willebrand disease infused with plasma from patients with hemophilia A. This suggests that the defect in classic hemophilia involves some activating function of another substance which is lacking in von Willebrand disease.

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* All five-digit numbers refer to number of entry in [1].

Among the enzymopathies, an example of nonallelic disorders with deficiency of the same enzymatic *function* may be provided by the glycogen storage diseases. In glycogen storage disease V (McArdle disease, 23260), a deficiency of muscle phosphorylase is found. Although no such instance has been proved, deficiency of muscle phosphorylase *b* kinase would be expected to produce the same or a similar phenotype and would appear to be phosphorylase deficiency if appropriate assays were not done [27]. Autosomal recessive inheritance of McArdle disease is well substantiated, but an excess of affected males reported is consistent with the existence of an X-linked recessive form; muscle phosphorylase *b* kinase in mice is determined by an X-linked gene. Hepatic phosphorylase *b* kinase deficiency (glycogen storage disease VIII, 30600) is indeed X-linked. Deficiency of hepatic phosphorylase is characteristic of glycogen storage disease VI (Hers disease, 23270). Here again glycogen storage disease VIII could be misinterpreted as phosphorylase deficiency rather than phosphorylase kinase deficiency.

Although the existence of structural change in the same polypeptide chain is strong support of allelism, structural change in different polypeptide chains does not exclude allelism because it is possible that, in the change of an enzyme or other protein from an inactive form in which it is synthesized to an active form, a proenzyme or other precursor is cleaved. An example is plasmin, whose main function is digestion of fibrin in blood clots and which is formed from plasminogen by the proteolytic cleavage of an arg-val bond resulting in a molecule which has two chains held together by a disulfide bond. Insulin is another example; it consists of two polypeptide chains formed from one, proinsulin, by enzymatic cleavage of a region which connects the carboxyl end of the B chain to the amino end of the A chain. The A and B chains in insulin are linked by two disulfide bonds.

COMPLEMENTATION IN THE DEMONSTRATION OF NONALLELISM

Physiologic complementation is another proof of nonallelism. Lack of complementation is necessary but not sufficient evidence of allelism. This type of evidence for nonallelism or allelism among the several forms of mucopolysaccharidosis was provided by Neufeld and Fratantoni's [28] in vitro study of fibroblasts. An older example is the X-linked hemophilias. Serum from some pairs of cases cross-correct (hemophilias A and B) whereas other pairs of cases (the allelic forms of the same disorder) do not cross-correct even though the clinical picture is rather different, in severity at least. Before the cross-correction observations were made, all X-linked hemophilias might have been considered to be determined by a single locus.

Molecular complementation (or lack thereof) is also a method for demonstrating allelism versus nonallelism. This approach, called dissociation and recombination, was introduced by Itano and Robinson [29] for the study of hemoglobin variants and has been used relatively extensively to distinguish members of the α and β allelic series. Recombination of acid- or alkali-dissociated α and β chains of the particular variant human hemoglobin under study with similarly dissociated α and β chains of canine hemoglobin proved particularly useful [30]; canine hemoglobin is available in ample quantities and differs from human hemoglobin in both chains so that the human/canine recombinant forms are likely to have different electrophoretic mobility whether the human variant is in the α or β chain. A similar approach has not yet been used in demonstrating nonallelic heterogeneity in an enzymopathy.

Cell hybridization is another means of complementation. Clinically different forms of xeroderma pigmentosum (27870) have been found to have different degrees of deficiency of the DNA-repair enzyme and therefore are listed in table 1 as possibly allelic forms. However, complementation studies by the method of cell hybridization [31] indicate that the usual xeroderma pigmentosum and the deSanctis-Cacchione syndrome ("xerodermic idiocy," 27880), which have functional deficiency of the same enzyme and might plausibly be considered allelic despite the difference in phenotype, are, in fact, complementary and presumably nonallelic. When cells from the two types are fused, enzyme activity is restored. Although there are presumably allelic varieties of galactosemia, such as those produced by the gal^{0} and gal^{Duarte} genes [32], the cell-hybridization studies of Nadler, Chacko, and Rachmeler [33] suggest the existence of nonallelic forms of galactosemia. (Although these authors favored interallelic complementation to explain their findings, nonallelic complementation would seem equally, if not more, likely.) In the next few years we will undoubtedly see much use of cell hybridization to answer the question of allelism.

OTHER APPROACHES TO DEMONSTRATION OF ALLELISM

Cystinuria illustrates another approach to the proof of allelism. It occurs in three apparently allelic varieties, I, II, and III, identified on the basis of the findings regarding renotubular and intestinal transport function in homozygotes and heterozygotes (table 3). Patients can, furthermore, be shown to be genetic compounds when studies of heterozygotes on the two sides of the family indicate that the forms introduced by the two parents are different. The fact that different genes combined in the offspring produce disease supports allelism.

A similar "interacting" or "noninteracting" argument is used for allelism or nonallelism in the thalassemias and hemoglobinopathies. In the presence of Hb S, β-thalassemia is an interacting form. The person heterozygous for both β-thalassemia and Hb S has a distinctive disorder previously known as microdrepanocytosis. Other evidence indicated that β-thalassemia is allelic with Hb S (or pseudoallelic, i.e., very closely linked). The person heterozygous for both α-thalassemia and Hb S is asymptomatic. This line of reasoning is invoked by my colleagues and me [35] to support the allelism of the achondroplasia and hypochondroplasia genes. In a family in which the father has achondroplasia and the mother has hypochondroplasia, an offspring has a skeletal dysplasia milder than homozygous achondroplasia but probably more severe than any case of heterozygous achondroplasia. We suggest

TABLE 3

Possibly Allelic Forms of Cystinuria (22010)

1. Cystinuria I	
Homozygote:	In urine large amounts cystine, lysine, arginine, ornithine
Heterozygote:	No aminoaciduria
2. Cystinuria II	
Homozygote:	Same as cystinuria I
Heterozygote:	Moderate aminoaciduria, mainly cystine and lysine
3. Cystinuria III	
Homozygote:	Same as cystinuria I and II, but intestinal transport not impaired as it is in I and II
Heterozygote:	As in cystinuria II
Genetic compounds:	I-II, I-III, and II-III identified by family studies

Source.—After Rosenberg [34] and others.

that the child represents the achondroplasia/hypochondroplasia genetic compound. This form of evidence can be considered at best only suggestive. It is, however, not possible to enumerate many examples of nonallelic interaction. We or others have, for example, observed patients with the following noninteracting combinations of dominant traits: (1) hereditary hemorrhagic telangiectasia (18730) and elliptocytosis (13050 or 13060); (2) achondroplasia (10080) and neurofibromatosis (16220); (3) achondroplasia and X-linked vitamin-D-resistant rickets (19310); (4) neurofibromatosis (16220) and familial colonic polyposis (17510); (5) osteogenesis imperfecta (16620) and parastremmatic dwarfism (16840); (6) Peutz-Jeghers syndrome (17520) and polycystic kidneys (17390); (7) tuberous sclerosis (19110) and neurofibromatosis (16220); (8) acanthosis nigricans (10060) and hereditary hemorrhagic telangiectasia (18730); (9) neurofibromatosis (16220) and Ehlers-Danlos syndrome (13000); (10) myotonic dystrophy (16090) and polycystic kidneys (17390). That there was no evidence of interaction in any of these speaks against allelism; indeed, the third pair of traits are confidently known to be on different chromosomes, the X and an unspecified autosome.

Sometimes classical genetic methods can demonstrate allelism versus nonallelism. If two persons affected by seemingly different recessive diseases married and had all affected children this would be evidence of allelism even if the phenotypes of the children (genetic compounds) were different from that of either parent. Conversely, if the parents had different recessive phenotypes which seemed to be allelic because deficiency of the same enzyme function was demonstrable, allelism would be disproved if all progeny were normal.

Linkage can disprove allelism, although it cannot prove it. The classic examples are elliptocytosis, which is known to exist in at least two nonallelic varieties linked or unlinked to the Rh blood group locus [36], and hemophilias A and B, which are linked and unlinked, respectively, to the G6PD and colorblindness loci [37]. Most of the disorders listed in table 1, part I,A are autosomal recessive conditions which are not efficiently studied by classical linkage methods available in man. For the dominant and for X-linked recessive conditions listed in table 1, parts I,B and II,B, however, nonallelism might be sought by linkage test.

SOME SPECIFIC EXAMPLES

The lysosomal disorders seem especially prone to having two or more phenotypically rather diverse forms of the same enzyme deficiency. In addition to MPS I (iduronidase deficiency), listings I,A: 2, 9, 11, 14, 18, 21, 23, 27, 28; I,B,4; and II,A,1 and 6 in table 1 are known lysosomal diseases; others such as I,B,10 and 12 may be. This is possibly a disproportionate representation. The several forms of G_{M1}-gangliosidosis (23050, 23060) and G_{M2}-gangliosidosis (27280, 26880, 23070)—also lysosomal diseases—are not listed, because, although the same enzyme is deficient, different isozymes are involved, and the molecular and genetic relationships are not clear. Furthermore, the existence of phenotypically distinctive forms of Krabbe disease with deficiency of the same enzyme, galactocerebroside β-galactosidase, is sufficiently uncertain that this lysosomal disease has also not been listed.

Crocker's types A and B of Niemann-Pick disease (otherwise known as the infantile and visceral forms, respectively) are clinically very different. No quantitative or qualitative difference has been identified in sphingomyelinase, which is deficient in both. Metachromatic leukodystrophy provides an even more striking example from among the lysosomal diseases. The late infantile form has onset usually before age 30 months and death before age 5 years. Motor symptoms are followed by mental deterioration. The adult form of metachromatic leukodystrophy has onset after age 16 with psychosis as the initial manifestation. Cases with an intermediate age of onset (8–16 years) may represent the genetic compound. Cerebroside sulfatase is deficient in all three forms. Porter et al. [38] have shown in vitro functional differences in fibroblasts from the late infantile and adult forms.

Parts I,B and II,B of table 1 list disorders in which the nature of the basic biochemical defect is not known but allelism can be suspected with some plausibility. Cystinosis, for example, occurs in two major forms: an infantile malignant form and an adult benign type. These may be allelic and the juvenile form may represent the genetic compound, but no proof of this interpretation is yet available.

Unfortunately, space does not permit a discussion of the various forms of each of the disorders listed in table 1. Many have phenotypic differences as striking as those just mentioned. These aspects will be described in the 1973 edition of *Mendelian Inheritance in Man* under the entry numbers given in table 1.

SUMMARY

Alleles can produce quite different disorders. The most conclusive proof of allelism available in man is the demonstration that the disorders in question are the result of different amino acid substitutions in the same polypeptide chain. Complementation, physiologic or molecular or by cell hybridization, is convincing proof of nonallelism; failure of complementation suggests but usually does not prove allelism. Differences in heterozygote expression (as in cystinuria) and interaction (as in the

thalassemias and the cystinuric mixed heterozygotes) provide further evidence on allelism.

ACKNOWLEDGMENTS

For many stimulating and productive discussions, I am indebted to Drs. Thaddeus E. Kelly and David C. Siggers, to Mr. Leslie J. Krueger, and to many others.

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